EXHIBIT B

SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 2**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF JIMMY W. MAYS

I. QUALIFICATIONS

Jimmy W. Mays

In 1979, I received my bachelor of science (BS) in Polymer Science from the University of Southern Mississippi. My CV is attached at Exhibit A. After receiving my B.S. from the University of Southern Mississippi, I started my graduate studies in Polymer Science at the University of Akron, the largest and arguably the best polymer science program in the country, where I received my Ph.D. in Polymer Science in 1984. The title of my Ph.D. thesis is "Characteristic Ratios of Model Polydienes and Polyolefins". This work involved the synthesis of well-defined polydienes of controlled microstructure and the subsequent hydrogenation of these materials to obtain model polyolefins, including polypropylene. The conformational characteristics of these materials were studied by a variety of characterization techniques, including gel permeation chromatography (GPC), differential scanning calorimetry (DSC), nuclear magnetic resonance spectroscopy (NMR), and Fourier transform infrared spectroscopy (FTIR).

From 1983-1987, I worked as a research chemist at Hercules Incorporated at their central R&D facility in Wilmington, Delaware. At the time, Hercules was one of the largest producers of polypropylene in the world. For most of my time there I worked in a Polymer Characterization Group, where we performed molecular weight and molecular size measurements on a wide range of polymers, including water soluble polymers and

polyelectrolytes, semi-crystalline polyolefins, especially polypropylene, and organosoluble polymers and copolymers. GPC was used extensively in this work. During this time, I was also the official "technical liaison" between the Hercules Fibers Technical Center (FTC) in Oxford, GA, where polypropylene fiber was produced, and Hercules central R&D facility. My responsibility was to visit FTC regularly and help the workers at FTC solve their technical problems by using central research expertise and facilities.

In 1988, following my employment at Hercules Incorporated, I joined the faculty at the University of Alabama at Birmingham (UAB) as an Assistant Professor in the Department of Chemistry. In 1992, I was promoted to Associate Professor and in 1995 was promoted to Professor of Chemistry. A major focus of my research activities at UAB was on polymeric biomaterials.

I am currently a Distinguished Professor of Chemistry at the University of Tennessee. I am also a Distinguished Scientist at the Oak Ridge National Laboratory and continue to serve as an Adjunct Professor at UAB. I also hold an appointment as Professor in the University of Tennessee, Institute of Biomedical Engineering. For the last thirty plus years, my research has focused on the synthesis and analytical characterization of linear and branched polymers and copolymers, including polypropylene. I have developed new polymeric materials for a host of applications, including new elastomers, new polymeric membranes for water purification and fuel cells, and new biomaterials.

I have published about 380 peer-reviewed papers in various scientific journals. I would estimate that well over half of these papers involve the use of GPC to characterize polymer average molecular weights and molecular weight distributions. The great majority also rely on methods including spectroscopy, microscopy, and mechanical properties measurements to characterize the polymers. These publications include work on polypropylene.

I, with Dr. Howard Barth, edited the book *Modern Methods of Polymer Characterization*, an often cited book on polymer characterization techniques, including GPC (Barth HG, Mays JW (Eds.), *Modern Methods of Polymer Characterization*, Wiley-Interscience (1991)) ("Barth and Mays"). I have also written invited chapters for the *Handbook of Polyolefins*, both the first edition in 1993 [1] and the second edition in 2000 [2], on characterization of polyolefins, including polypropylene. I am presently under contract with John Wiley & Sons to edit a 2nd edition of *Modern Methods of Polymer Characterization*.

I have worked extensively in the area of polymeric biomaterials, with many peer reviewed papers, a patent, and another patent pending, and I was a member of the Society of Biomaterials for several years. My work in this area includes development of novel bone cements, dental biomaterials, tissue engineering, drug delivery systems, surgical sealants, and polypropylene pelvic mesh.

Throughout my professional career I have received numerous honors and awards. In 2001 I received the Caroline P. and Charles W. Ireland Prize for Scholarly Distinction (UAB's highest award to faculty in the arts and sciences). In 2001, I was named University Scholar at UAB (honorary faculty status granting maximum latitude in conducting interdisciplinary teaching and research). Other recent honors include: 2003 Arthur K. Doolittle Award, Polymeric Materials Science and Engineering Division, American Chemical Society; 2006 Named Honorary Professor by East China University of Science and Technology; 2007 Chair, Polymers West Gordon Research Conference; 2008 Distinguished Service Award, ACS Division of Polymer Chemistry; 2009 Bayer Lectures on Polymers, Cornell University; 2009 Southern Chemist Award of ACS (top chemist in Southeastern US); 2010 Named Founding POLY Fellow, ACS Division of Polymer Chemistry; 2011 Herman Mark Senior Scholar Award, ACS Division of Polymer Chemistry; 2011 Outstanding Alumni Award, University of Akron; 2011 Fellow, American Chemical Society; 2012 Fellow, ACS Division of Polymeric Materials Science and Engineering; 2012 Fellow, American Association for the Advancement of Science; 2013 Bill & Melinda Gates Foundation Grand Challenges Explorations Award; 2014 Fellow of the Royal Society of Chemistry.

Through my tenure as an academic faculty member at both UAB and the University of Tennessee, I have taught numerous graduate-level and undergraduate-level Polymer Chemistry and Polymer Materials classes. For 14 years at UAB I taught a two semester course on Polymeric Materials which was taken annually by upper level undergraduates and graduate students in Chemistry, Materials Science and Engineering, and Biomedical Engineering. In this class, the theory and principles of polymer characterization techniques (GPC, spectroscopy, microscopy, mechanical properties) were taught. There were required, even for graduate students, laboratories on SEC and on spectroscopy. This fall, I developed and taught a new laboratory based course, Advanced Techniques in Polymer Synthesis and Characterization, taken by 2nd year graduate students pursuing the Ph.D. in polymer chemistry.

I am a member of the American Chemical Society and its PMSE (Polymeric Materials Science and Engineering) and POLY (Polymer Chemistry) Division, and I am a member of the American Association for the Advancement of Science and the Society for Biomaterials. I have at times in my career been a member of the American Physical Society.

I currently serve as an Associate Editor for the *International Journal of Polymer Analysis and Characterization*. I previously served as an editor of *European Polymer Journal*. I serve or have served on the editorial advisory boards of various journals including, *Macromolecules*, *Polymer Bulletin*, *Journal of Applied Polymer Science*, and *European Polymer Journal*. I also review approximately 50 papers/proposals annually for various journals and agencies including *Journal of Applied Polymer Science, Macromolecules, Journal of Polymer Science, Journal of Physical Chemistry, Journal of Chemical Physics, Journal of the American Chemical Society, Angewandte Chemie, Polymer Degradation and Stability, Soft Matter*, National Science Foundation, Department of Defense, American Chemical Society/Petroleum Research Fund, Department of Energy, and others.

Since 2000, I have been a member of the Governing Board for the International Symposium on Polymer Analysis and Characterization (ISPAC). ISPAC annually holds an international meeting that addresses forefront issues in all areas of polymer characterization. I have previously chaired and hosted an ISPAC Meeting in Oak Ridge, TN.

The materials I considered in preparing the statements below are listed in Exhibit B.

II. BACKGROUND

Ethicon sells permanently implantable polypropylene-based meshes intended to treat Stress Urinary Incontinence (SUI) and Pelvic Organ Prolapse (POP). These devices are manufactured from Prolene resin, which is Ethicon's proprietary blend of polypropylene that was originally developed for use as a suture material in the 1960's and is currently used to manufacture all of Ethicon's polypropylene-based mesh products. These products include Prolene Mesh, Gynemesh PS, Gynecare Prolift, Gynecare Prolift + M, Prosima, Gynecare TVT System, Gynecare TVT Retropubic System, Gynecare TVT Obturator (TVTO), Gynecare TVT Abbrevo, Gynecare TVT Secur, and Gynecare TVT Exact. This report is an assessment of the characteristics and performance of Prolene, the polypropylene, and the mesh, cut into various shapes and

configurations for different anatomic sites and insertion methods, and utilized in the listed Ethicon devices used to treat Stress Urinary Incontinence (SUI) and Pelvic Organ Prolapse (POP).

This report focuses on the following key issues: the chemical structure and properties of polypropylene, degradation of polypropylene by thermo-oxidative processes and *in vivo*, and effect of *in vivo* degradation on the polypropylene implant.

III. SUMMARY OF OPINIONS

1) It has been well understood for many years that polypropylene is susceptible to oxidation and it degrades by an oxidative mechanism in the body, resulting in chain scission and diminished mechanical properties (reduced compliance and brittleness). These facts are clearly documented in the peer reviewed scientific literature. Ethicon did not take into account polypropylene's propensity for oxidation during design of its various Prolene based mesh products.

2) The mesh is intended to last for the lifetime of the patient, but the addition of antioxidants to the Prolene polypropylene does not permanently prevent mesh degradation, and thus it is not possible to guarantee that the mesh will function properly after implantation;

3) Ethicon was aware of the oxidation of Prolene prior to the introduction of the transvaginal mesh devices sold by Ethicon to the marketplace, but the company did not consider the risks associated with polypropylene oxidation on the stability of the Prolene mesh, to the detriment of patients implanted with the various devices made from the polypropylene resin;

4) Foreign body reaction to the mesh *in vivo* leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking;

5) PP mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee.

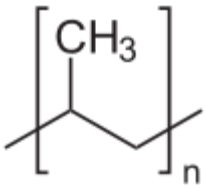
6) Thus, the Prolene mesh is unreasonably dangerous, defective and is not suitable to serve as the permanent implants that they have been represented by Ethicon to be.

IV. OPINIONS

Section 1.0 Polypropylene:

Overview

Polypropylene is a synthetic polymer made by addition polymerization of the monomer propylene, CH_3-CH=CH_2.



Scheme 1: The repeating unit in polypropylene

Propylene is a byproduct of oil refining, to produce gasoline, and natural gas processing. During oil refining, ethylene, propylene, and other compounds are produced as a result of "cracking" larger hydrocarbon molecules to produce smaller hydrocarbons that are more in demand. Ethylene and propylene are used in vast quantities to produce polyethylene and polypropylene, the two largest volume plastics in the world (currently about 60% by weight of the world's polymer production). Polypropylene is a thermoplastic polymer (meaning it softens and flows upon heating above its melting point), allowing it to be formed into useful objects such as fibers, used in a wide range of applications including textiles, ropes, fibers and fishing line, carpets, stationery, plastic parts, plastic containers, films and packaging, laboratory equipment, automotive components, etc.

Classifications of Polypropylene

Polypropylene may be classified according to its stereochemistry or tacticity. By far the most important type of polypropylene is isotactic polypropylene, which is made using Zeigler-Natta or metallocene catalysts. Isotactic polypropylene, because of the regular orientation of the methyl (-CH_3) substituents on each repeating unit, is a semi-crystalline polymer with a melting

point of about 165 °C. This high melting temperature allows polypropylene to be autoclaved, and the crystallinity present in the polymer imparts dimensional stability and solvent resistance.

Additives in Polypropylene

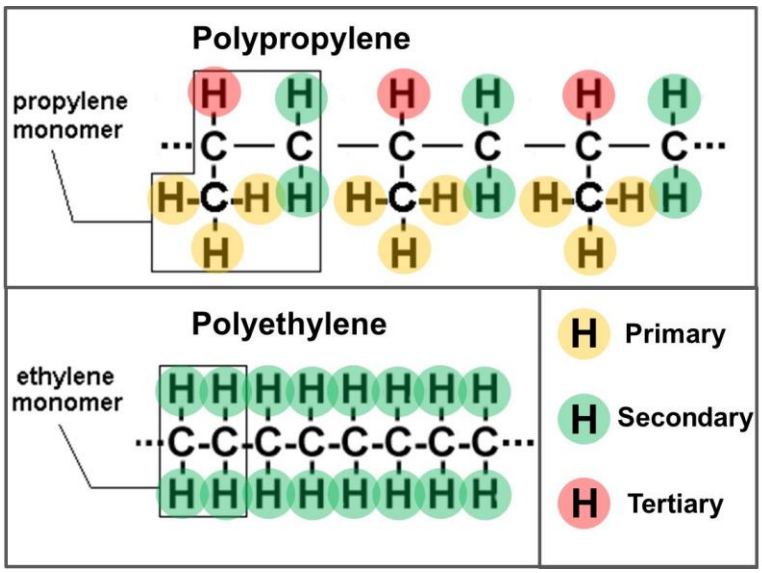
Commercially produced polypropylene is almost never pure polypropylene. A range of additives are added [3] depending on the anticipated application of the material. Common additives include antioxidants, UV stabilizers, antistatic agents, electrically conducting additives, fillers, pigments and colorants, lubricants, nucleating agents, polymer processing aids such as fluoroelastomers, and transition metal scavengers such as calcium stearate in order to deactivate residual catalyst (which is not removed from the polypropylene).

Degradation of Polypropylene

Polypropylene is highly susceptible to oxidative degradation, which can reduce the molecular weight of the polymer and diminish mechanical properties. Such oxidation occurs even at ambient temperature, although it is accelerated at higher temperatures, and it leads to a rapid deterioration of the physical properties over a period of weeks [3,4]. While all polyolefins are susceptible to oxidative degradation, polypropylene is the most susceptible – Vasile states [ref 3, p. 517] that "…PP products could not even exist without the addition of stabilizers." Her meaning reflects the fact that PP is so unstable in the presence of oxygen or other oxidizing chemical species that products made of PP would lose their mechanical integrity so quickly as to be unusable. Thus, antioxidants and other stabilizing additives are nearly always added to polypropylene.

Mechanism of Oxidative Degradation of Polypropylene

All polyolefins, including polyethylene and polypropylene, are susceptible to oxidation. Oxidative degradation of these hydrocarbon polymers should come as no surprise to any scientist or engineer that has taken second year college chemistry, because they are members of the family of hydrocarbons known as alkanes. Oxidative degradation of alkanes is a fundamental reaction that is taught in every organic chemistry textbook [4]. These oxidation reactions involve oxygen or other oxidizing chemical species attacking carbon-hydrogen bonds in the polyolefins. In polyolefin chemical structures, hydrogens are classified as primary, secondary, or tertiary depending upon where the carbon they are connected to is located in the structure. The schematic below shows the polypropylene chemical structure with primary, secondary and tertiary hydrogen atoms indicated.



Scheme 2: Structures of Polypropylene and Polyethylene Identifying Primary, Secondary and Tertiary Hydrogen Atoms.

The tertiary hydrogens present on each repeating unit of polypropylene make this polymer particularly susceptible to oxidative degradation via a free radical mechanism. Primary and secondary hydrogens are less susceptible to oxidation. For comparison the structure of a more oxidatively stable polyolefin, polyethylene, is show. It is more stable because it contains no tertiary hydrogens, only secondary ones. The oxidation mechanism of polypropylene involves initially the chemical reaction of oxygen, O_2, with these tertiary sites to form hydroperoxides along the polymer backbone. The detailed mechanism is complex, but these hydroperoxides then decompose to form free radical species that break chemical bonds by attacking other sites along the polymer chain. There are several paths that lead to chain scission with accompanying formation of carbonyl groups (carbon – oxygen double bonds) [5-7].

The basic mechanism of polypropylene's oxidative degradation is shown below [6]. Here R is used to represent the polypropylene chain. RH represents a tertiary hydrogen atom attached to the rest of the polypropylene molecule.

Scheme 3: Initiation:

$$RH + O_2 \rightarrow ROOH$$

$$RH + O_2 \rightarrow R\cdot + HOO\cdot$$

$$ROOH \rightarrow RO\cdot + HO\cdot$$

$$R\cdot + O_2 \rightarrow ROO\cdot$$

In the first step, the polypropylene chain reacts with molecular oxygen (O_2) to form a hydroperoxide, which can then form various free radical species (highly reactive compounds that contain unpaired electrons indicated by " ·").

Scheme 4: Propagation and Radical Transfer:

$$ROO\cdot + RH \rightarrow ROOH + R\cdot$$

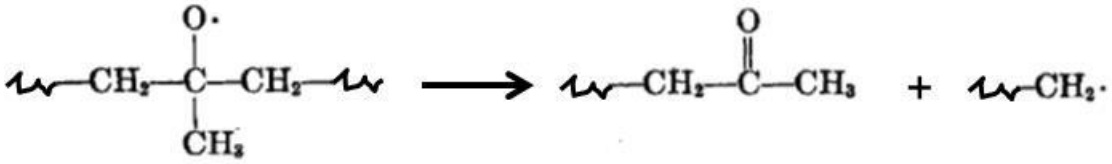
$$RO\cdot + RH \rightarrow ROH + R\cdot$$

$$HO\cdot + RH \rightarrow H_2O + R\cdot$$

In these reactions, the free radical species formed during initiation react with other polypropylene chains, creating new free radical sites on them. These reactions form hydroperoxides (ROOH) and hydroxyls (ROH), which may be detected by methods like Fourier transform infrared spectroscopy (FTIR) and are indicators of polypropylene oxidation.

Disproportionation:

The formed free radical species may terminate by radical coupling or by disproportionation. Disproportionation is believed to be the primary termination mechanism, leading to the formation of aldehydes, ketones, and carboxylic acids, with accompanying chain cleavage [8]. FTIR spectroscopy can be used to detect the presence of these types of functional groups [7]. An example of a typical disproportionation reaction during polypropylene oxidation, leading to the formation of a ketone with accompanying polypropylene chain cleavage (one PP chain is broken into two), is shown below [8]. In this more detailed chemical equation the initial structure on the left-hand-side corresponds to the species RO· Schemes 3 and 4. The reaction shown below is an alternative chemical pathway for the reaction of RO· to those shown in the other two schemes. During oxidative degradation of PP, all of these chemical reactions occur simultaneously.



Scheme 5: Typical Disproportionation Reaction on Polypropylene Leading to Chain Cleavage. Wiggly lines indicate continuation of the rest of the PP chain.

In the presence of UV light, which provides enough energy to break chemical bonds, the oxidative process is accelerated. Chromophores present in polypropylene during fabrication, storage, and processing are believed to play a key role in the initiation of photodegradation [5].

The morphology of polypropylene (crystalline versus amorphous regions) also plays an important role in oxidative degradation. Oxidation occurs preferentially at the surface of the material where there is more oxygen. Oxidation also occurs within the amorphous regions of semi-crystalline polypropylene but not within the crystalline domains where the dense packing of the chains prevent oxygen penetration. Thus the amorphous regions between crystalline domains may be eroded away by oxidation, leading to the formation of micro-cracks in the material with accompanying degradation of mechanical properties [5].

In vivo Degradation of Polypropylene

Living organisms can chemically attack synthetic polymers. Both salts and enzymes present in the body catalyze degradation of polypropylene in biological media. Salts, especially phosphates, catalyze processes leading to the degradation of polymers containing carbonyl groups [9]. Carbonyl groups may exist in the polypropylene due to oxidation prior to implantation, and they are known to be introduced into polypropylene *in vivo* [7] through the action of enzymes. Polypropylene capsules implanted in rats show enzyme activity on their surfaces, involving acid phosphates aminopeptidase, and oxyreductase, after 7 days, with an increase in enzyme activity after 14 days, associated with increased phagocytosis in the region of the implant [9,10]. These processes reflect the natural response of the human body to attack foreign bodies and a scientific basis to understand the *in vivo* effect of the human body's response to a foreign body on polypropylene. Phagocytic cells respond to the injury to degrade debris and foreign materials prior to wound healing. Importantly, for polymer scientists looking at the *in vivo* effects on

polypropylene, it is well-established that the chemistry of phagocytosis involves these cells metabolizing oxygen and producing strong oxidants such as hydrogen peroxide and hypochlorous acid as the product of their foreign body response function [11].

Strong evidence suggests that the process of enzymatic degradation of polypropylene involves a free radical oxidative mechanism, the same as or analogous to those shown above, with oxygen being incorporated into the polymer, first as hydroxyl groups and then as carbonyls [7,9,12]. All evidence is consistent with a degradation mechanism involving oxidative enzymes and oxygen dissolved in the living medium [9]. The body recognizes polypropylene as a foreign substance, which causes an inflammatory response called the "foreign body reaction" [13]. In polypropylene implanted in rats, macrophages and FBGCs were found in both the implants and in the surrounding tissue [14]. Macrophages on the surface of the material fuse to form foreign body giant cells (FBGCs), resulting in secretion of high concentrations of highly reactive oxidizing species (peroxides, acids, enzymes) on the surface of the implant [13]. This foreign body reaction persists at the surface of the implant as long as the implant is in the body [13]. Thus polypropylene, which is known to be susceptible to oxidative degradation, is continually attacked by strong oxidizing agents inside the body.

Effect of Polypropylene Degradation *In Vivo*

Oxidative degradation of polypropylene causes chain scission – it literally breaks the polypropylene molecules apart. This degradation causes a reduction in the mechanical properties (resistance to breaking under load or strength) of the polypropylene since mechanical properties decrease when molecular weight is reduced [7,15]. Furthermore, the degradation starts at the surface of the implant where it is in contact with its surroundings, and the disordered amorphous regions of the polypropylene are particular susceptible.

The polypropylene used in pelvic repair meshes is semicrystalline. Figure 1, shows a schematic of semicrystalline polymer structure, obtained from a basic text in the field of polymer morphology [Ref. 16, Figure 1.2]. The discussion of semicrystalline polymer structure given below is based on this text. The 10 nm scale-bar had been added to provide an approximate idea of the size of these structures.

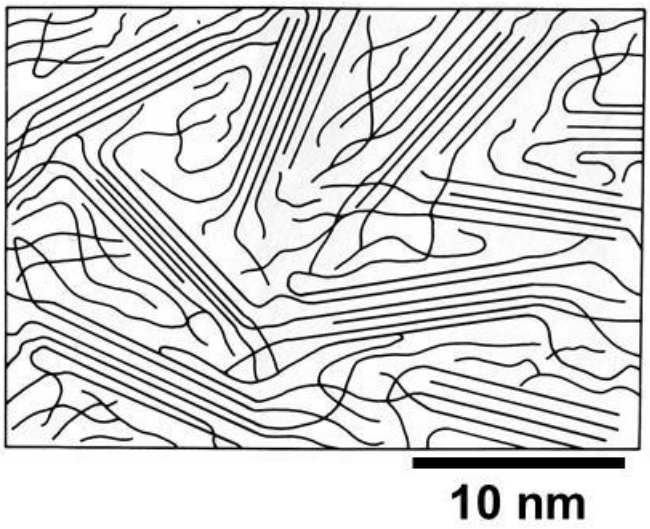


Figure 1: Schematic of Semicrystalline Polymer Morphology

The lines in Figure 1, represent polymer chains. In some parts of the structure the lines are straight and pack parallel to one another. These regions are crystalline; the polymer chains in these crystallites are locked into position relative to one another and resist deformation. In other parts of the structure, the polymer chains take wiggly conformations and are mixed together randomly. These regions are amorphous. The polymer chains in the amorphous regions can be deformed much more easily than those in the crystalline regions. The overall semicrystalline structure is a composite in which individual polymer chains go back and forth between crystallites and amorphous regions, thus tying these regions together. The amorphous regions give the polypropylene fibers the flexibility to bend and be deformed, for instance as they are bent in knitting a mesh structure, and they hold the crystallites together. At the same time, the crystallites regions provide strength, reinforcement and high temperature stability, which is important so the meshes can be sterilized by autoclave. This nanometer-length-scale semicrystalline, composite structure is critical to the properties of the PP fibers. This composite can only deliver the requisite properties as long as it remains intact, i.e. amorphous regions connecting crystallites together.

Figure 1 also suggests that the polymer chains in the amorphous regions are packed less densely than in the crystalline regions. This is true in the actual physical material. In the terminology of the polymer field, the amorphous regions are said to contain more "free volume" than the crystalline regions [17,18]. Free volume is the empty space between the polymer

molecules. The free volume in the amorphous regions allows oxygen and other oxidizing chemical species the space to diffuse into and penetrate the polypropylene structure. Thus, the degradation process erodes the amorphous polymer that bridges the crystallites and results in the formation of cracks in the early stages of implantation, with fragmentation (loss of particulates or peeling) at longer times [19-26]. In selectively removing the amorphous portion of the polypropylene, the part which gives polypropylene fibers their flexibility, the polypropylene becomes stiffer and embrittled [6,11,22,23,27,28].

It should also be noted that oxidation occurs at the surface of the material where it comes into contact with oxygen or oxygen containing substances. Thus, the geometry of the polypropylene implant is important. In articles with higher surface to volume ratios such as films and fibers, the physical properties deteriorate more rapidly upon oxidation [5].

Addition of Anti-oxidants to Polypropylene

As noted above, a number of additives are added to polypropylene in order to modify its properties for the particular application. Anti-oxidants, sometimes called stabilizers, are almost always added to polypropylene due to its high susceptibility to oxidative degradation. Anti-oxidants may be broadly classified as primary, those that work by reacting preferentially with oxygen or the oxidizing species forming stable free radicals, and secondary, those that work by decomposing hydroperoxides involved in the oxidative degradation process [3]. It is common to use a combination of primary and secondary anti-oxidants to stabilize polypropylene.

Prolene resin is Ethicon's proprietary blend of polypropylene that was originally developed for use as a suture material in the 1960's and is still used even today to manufacture all of Ethicon's polypropylene-based mesh products. In a 2003 memo from John Karl of Ethicon to D. Burkley of Ethicon it is stated that "The objective of every polymer resin run has been to duplicate the original formulation as exactly as possible, "warts and all". Hence, virtually no changes have ever been made in the chemistry…" of Prolene, which had a 35 year history of use at the time of the memo [29]. Ethicon's Prolene polypropylene, which is used to manufacture its pelvic mesh, contains Santonox R and dilaurylthiodipropionate (DLTDP). Santonox R is a hindered phenolic antioxidant used to protect Prolene during high-temperature processing (compounding and extrusion), while DLTDP is used to protect Prolene from oxidation during long-term storage. Neither of these anti-

oxidants is designed to protect Prolene from attack by reactive oxygen species generated in the human body in response to implantation of a foreign body.

Addition of anti-oxidants to a polymer cannot permanently prevent its oxidation. This is because the anti-oxidants are consumed as they serve their function of reacting with oxidizing species. Furthermore, the anti-oxidant is dispersed throughout the polymer and only the anti-oxidant at the surface, where the implant is attacked by reactive oxygen species, can protect the polymer until it is eventually exhausted. At this point the foreign body attack continues and the polypropylene resin is degraded with deterioration of its physical properties, stiffening, and cracking. The degradation exposes new surface which is again attacked by reactive oxygen species, and the cycle continues. The foreign body attack persists as long as the implant remains in the body [13].

While it might seem attractive to simply add more anti-oxidant to increase the lifetime of the implant, this is not feasible for two reasons. The additives themselves may prove toxic to the human body and only so much anti-oxidant can be added before the physical properties of the polypropylene are compromised. For example, the Materials Safety Data Sheet (MSDS) for DLTDP [30] states "This material is not intended for use in products for which prolonged contact with mucous membranes or abraded skin, or implantation within the human body is specially intended, unless the finished product has been tested in accordance with the Food and Drug Administration and/or other applicable safety testing requirements." The MSDS sheet for Santonox R [31] states "This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)", and the MSDS cautions regarding skin corrosion/irritation, serious eye damage/eye irritation, skin sensitization, and organ toxicity to the respiratory system [31].

The Choice of Polypropylene as a Material for a Permanent Vaginal Mesh Implant

In 1976 Liebert et al. [6] published a paper entitled "Subcutaneous Implants of Polypropylene Filaments" in the Journal of Biomedical Materials Research. Polypropylene filaments were implanted into hamsters for varying periods of time and upon removal they were characterized using infrared spectroscopy (IR) and dynamic mechanical testing. Their IR analysis showed that oxidative degradation begins to occur after only a few days for polypropylene filaments containing only a trace of phenolic anti-oxidant. Both hydroxyl groups and carbonyl

containing groups were observed by IR. Dynamic mechanical testing implied a loss of suppleness of the filament (increase in modulus), which verified in mechanical terms the oxidation observed by IR spectroscopy. Gel permeation chromatography (GPC) analysis indicated that some chain scission occurs during the first 70 days of implantation. Liebert calculated that under *in vivo* conditions the induction time for oxidation of polypropylene to begin should be far longer (on the order of 20 years) and speculated on reasons for the extremely rapid oxidation *in vivo* [6]. It is now well-known that the foreign body response, discussed above, is responsible for the continual release of strong oxidizing agents at the surface of the implant [13]. In Liebert's study [6] oxidative degradation could be suppressed over the limited time period of the study by adding larger amounts of a hindered phenolic anti-oxidant (primary anti-oxidant) and a sulfur-containing synergist (secondary anti-oxidant).

In 1979 Postlethwait [32] implanted polypropylene sutures in the abdominal wall muscles of rabbits and recovered specimens over intervals from 6 months to 5 years. The polypropylene sutures showed fragmentation in 4% of the sutures examined and the perisutural formation of bone, cartilage or both in 2.6%. This author concludes "Although in most operations these minutiae of tissue reaction concerning polypropylene are of little consequence, it may be necessary to conduct further studies to determine if they have any significance."

In 1986 Jongebloed and Worst [19] used scanning electron microscopy (SEM) to examine a polypropylene surgical suture (supplier not identified) that had been in a human eye for 6.5 years. The suture showed cracks perpendicular to the longitudinal axis of the suture; part of the surface layer was nearly detached or completely missing; while the diameter of the suture was decreased at both ends by over 50% in comparison with the original diameter. The degradation was believed to be caused by the enzymatic actions of tissue fluids. The same group, in a separate paper the same year [20], reported a SEM study on a Prolene (Ethicon) suture that had been implanted in the human eye for one year. The reported that "both Prolene loops showed severe degradation of the surface layer."

In 1998 Mary et al. [21] reported a study that compared the *in vivo* behavior of poly(vinylidene fluoride) and polypropylene (Prolene, Ethicon) sutures used in vascular surgery.

"After 1 and 2 years *in vivo*, the explanted polypropylene sutures showed visible evidence of surface stress cracking.

In 2007 Costello et al. [22,23] studied explanted polypropylene hernia meshes (produced by C.R. Bard and Ethicon) by a variety of techniques and concluded "Cracks and other surface degradations such as peeling of the fibers are indicative of the oxidation of polymeric materials." They also remarked "Polypropylene is highly susceptible to the oxidative effects of the metabolites produced by phagocytic cells during the inflammatory response." And "…polypropylene is susceptible to oxidation, resulting from exposure to strong oxidants such as hydrogen peroxide and hypochlorous acid. These byproducts of the inflammatory response may degrade and embrittle the material, causing it to become rigid." And "Polypropylene is susceptible to oxidation due to its chemical structure" and results in deterioration of its physical properties *in vivo*. Degradation causes surface cracking, mesh contraction, loss of mass, embrittlement, decreased melting temperature, foreign body reactions and reduced compliance of the material. They observed the explanted polypropylene fibers using SEM and noted that "Micrographs of 79% of all explanted specimens exhibited cracks in the transverse or longitudinal direction." Figure 2 shows an SEM image from Costello [Ref. 23, Fig. 5] in which this cracking is evident.

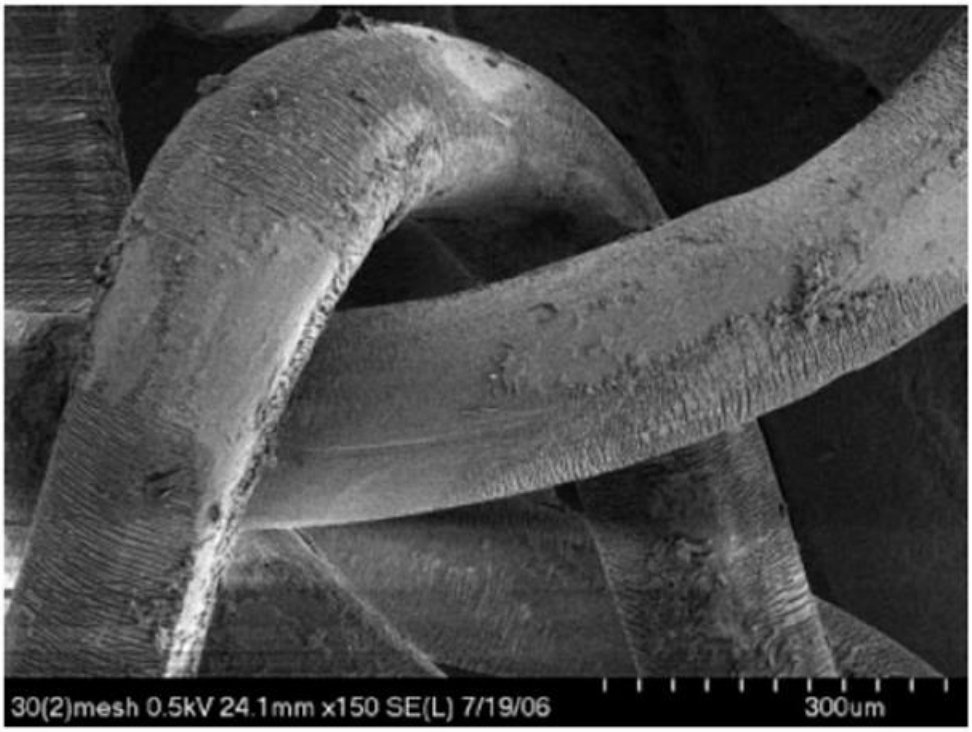


Figure 5. SEM of an explanted polypropylene mesh with transverse cracks.

Figure 2: SEM Image Reproduced From Costello [Ref. 23, Fig. 5] showing transverse cracking indicative of degradation due to oxidation.

At about the same time, Bracco *et al.* [33] also used SEM to observed explanted PP mesh fibers produced by various manufacturers and used in hernia repair and reported transverse cracking as characteristic of the damage they observed. Figure 3 is an SEM image of this cracking in PP fiber reproduced from Bracco [Ref. 33, Fig. 3]. Bracco [33] postulated that the primary cause of the cracked and degraded morphology of the PP fibers was absorption of small organic molecules of biological origin including cholesterol, squalene, and esterified fatty acids.

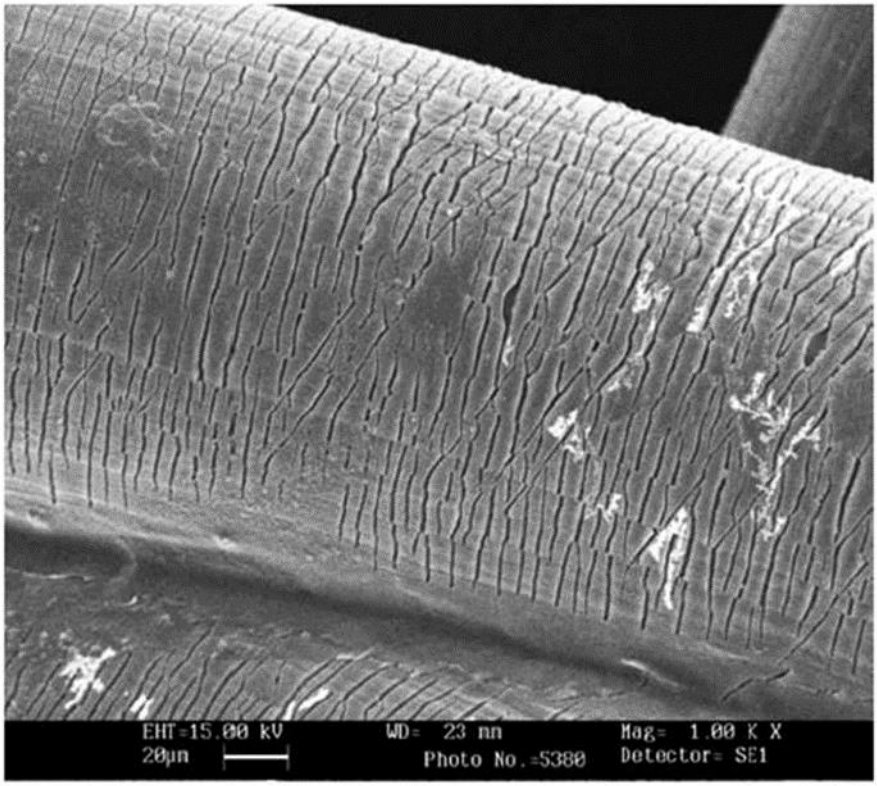


Fig. 3 Scanning electron microscopy (SEM) micrograph (1,000×) of fragment #9 polypropylene (PP)

Figure 3: SEM image of explanted PP fiber from Bracco [33]

Clave *et al.* in 2010 published a paper entitled "Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants" [24]. They reported polypropylene pelvic mesh damage including "superficial degradation, which appeared as a peeling of the fiber surface, transverse cracks in the implant threads, significant cracks with disintegrated surfaces and partially detached material, and superficial or deep flaking." Figure 4 shows three SEM images from Clave [Ref. 24, part of Fig. 1] showing the transverse cracking they reported as characteristic of degradation of explanted PP fibers due to oxidation.

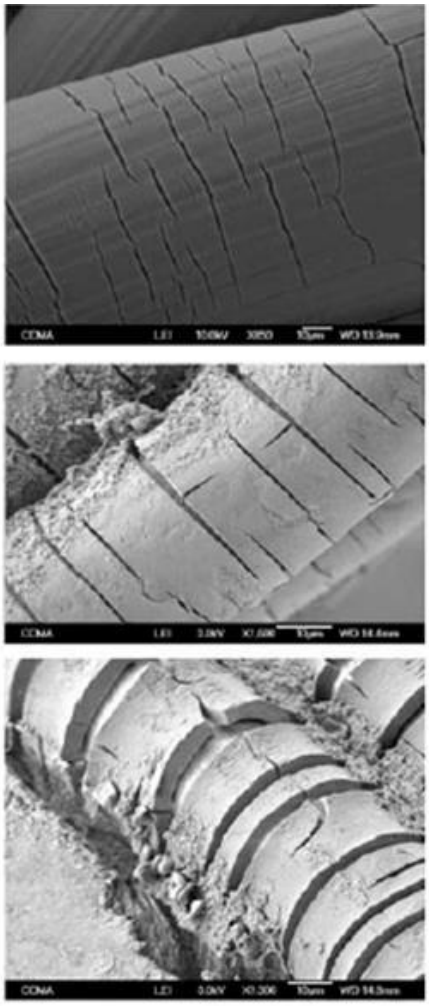


Figure 4: SEM of Transverse Cracking in Explanted PP Fibers from Clave [Ref. 24, part of Fig. 1]

Lefranc et al. [34] concluded that PP fiber meshes degrade when implanted for pelvic wall support, and cited transverse cracking as observed by SEM on explants as a characteristic identifier of this degradation. Lefranc [Ref. 34, Fig. 25.9] published a dramatic image of this cracking in explanted PP fibers, which he attributes to Clave, but which was not published in Clave's study [24]. This image taken by Clave, but published by Lefranc, is shown in Figure 5.

Fig. 25.9 SEM observation of degraded PP mesh under septic environment

Figure 5: SEM image of explanted PP mesh fibers with transverse cracking indicative of degradation [34].

As noted above, based on experiments in which degraded explanted PP fibers were extracted with hexane, Bracco [33] postulated that the primary cause of the cracked and degraded morphology of the PP fibers was their absorption of small organic molecules of biological origin including cholesterol, squalene, and esterified fatty acids. Subsequent researchers (Clave [24]; Lefranc [34]) have mentioned Bracco's small organic molecule hypothesis but have attributed degradation of the explanted PP fibers primarily to oxidation. Costello et al. [22,23] also attributed degradation observed in explanted polypropylene hernia meshes to oxidative degradation.

It is my opinion that Bracco has shown that some small, biologically derived organic molecules can be absorbed into the outer layers of implanted PP fibers. His study has not shown, however, that this process is the direct cause of fiber degradation, although it very well could be a contributing factor that aids oxidation. In the last paragraph of the *Discussion* section of their paper Bracco et al. try to explain their idea as to how absorption of small organic molecules could contribute to fiber degradation. The phenomenon that they are trying to explain is well known to

polymer scientists and is referred to as plasticization [35,36]. Plasticizers are small organic molecules that are absorbed into a solid polymer and soften it. The mechanism of this softening involves increasing the free volume space in amorphous regions of a solid polymer structure. The amorphous regions of the PP semicrystalline structure, as shown in Figure 1, are susceptible to plasticization by absorption of the types of biological, small organic molecules that Bracco observed. In particular esterified fatty acids are well known to plasticize polymers [37-39]. It is likely that an increase in free volume of the amorphous regions of implanted PP fibers due to plasticization from the absorption of small, biological organic molecules facilitates increased penetration into the PP fibers by oxygen and other oxidizing chemical species, thus accelerating PP fiber degradation due to oxidation.

Very recently Imel et al. [25] reported a study of *in vivo* degradation of polypropylene pelvic mesh (Boston Scientific) using methods specifically chosen to test whether or not oxidative degradation is responsible for observed changes in the mesh upon implantation. Both Fourier-Transform Infrared (FT-IR) spectroscopy and energy dispersive X-ray (EDS) spectroscopy showed clear signs of oxidative degradation. The EDS experiments were carried out within a scanning electron microscope (SEM) and were used to look for the presence of oxygen in polypropylene fibers (pristine polypropylene only contains carbon and hydrogen). EDS was also used to distinguish clean polypropylene fibers from biological tissues or fibers coated with biomaterial (biological material contains both oxygen and nitrogen, both of which can be detected in EDS). Thus the presence or absence of nitrogen in EDS was used as a discriminator of clean versus tissue contaminated fiber.

All explanted samples (implantation periods for the 11 samples ranged from 16-57 months) showed the presence of oxidation by both FT-IR and SEM/EDS [25]. The oxidative degradation was accompanied by cracking transverse to the fiber axis [25] as observed previously by other workers using SEM to examine explanted polypropylene hernia and pelvic mesh [20-24,33,34].

As discussed above, the oxidative degradation of polypropylene is known to cleave polymer chains, thereby reducing their molecular weight. Adequate amounts of 4 of the explanted samples were available to allow Imel et al. to characterize their molecular weights by gel

permeation chromatography (GPC). GPC showed significant reductions in weight-average and z-average molecular weights and a narrowing of the molecular weight distributions as compared to the same non-implanted material [25]. These changes in the molecular weight characteristic of the polypropylene are fully consistent with oxidative degradation and cannot be explained by absorption of small biological molecules [25]. Iakovlev et al. [26] recently carried out microscopic analysis of various explanted polypropylene meshes (from several suppliers including Ethicon), observed a degradation layer or "bark" and have proposed oxidative degradation as a mechanism consistent with their results.

Based upon all the published scientific studies discussed in this section, the step-by-step degradation process of polypropylene pelvic meshes *in vivo* may be summarized as follows: The implant causes increased activity by oxidative enzymes (foreign body response) in the vicinity of the implant. This leads to an oxidative degradation process that is evidenced by the appearance of hydroxyl and then carbonyl groups in the polypropylene, as observed by infrared spectra. There is accompanying degradation of the polypropylene molecular weight, and this process may be delayed, but not prevented, by the presence of anti-oxidants in the polypropylene. Anti-oxidants are preferentially consumed by the oxidizing species and over a period of months [25] their concentration falls below a level required to protect the polymer and oxidative degradation occurs [3]. This degradation is accompanied by a decrease in mechanical properties (embrittlement, loss of mass, decreased melting temperature, reduced compliance) of the polypropylene [3,23]. In particular, the surface and amorphous regions of the polypropylene are selectively degraded, resulting in cracks and, on longer exposure, fragmentation of the implant [22,25].

The change in materials properties of a material implanted in the female pelvis poses unreasonable risk of harm and is defective from a design perspective in terms of the material choice made by Ethicon. A polymer that cannot maintain its physical properties in its intended application is not a suitable choice for a reasonable engineer faced with polymer choices for the intended use as a permanently implanted mesh in the pelvis, as use of polypropylene may pose an unreasonable risk of harm to a patient. This is as a direct result of the degradation of the polypropylene fibers and its effect on the performance of the mesh due to embrittlement, stiffening, and tissue reaction cascade which may each affect the polypropylene and the tissues surrounding it *in vivo*.

In 2011 Ostergard [40] published an article entitled: "Degradation, infection and heat effects on polypropylene mesh for pelvic implantation: what was known and when it was known" The paper begins with the following two sentences: "Many properties of polypropylene mesh that are causative in producing the complications that our patients are experiencing were published in the literature prior to the marketing of most currently used mesh configurations and mesh kits. These factors were not sufficiently taken into account prior to the sale of these products for use in patients." The following are relevant facts, when they were known, and where they were published, obtained from Ostergard [40].

- "1953 Any implanted device must not be physically modified by tissue fluids, be chemically inert. [40 referencing 41].
- "1986 Degradation of PP suture known as seen with SEM." [40 referencing 19]
- "1998 PP mesh shrinks 30-50% after 4 weeks". [40 referencing 42]
- "2001 The abdominal wall stiffens after mesh insertion." [40 referencing 43]
- "2010 Degradation occurs in all currently used meshes." [40 referencing 24]

Thus as early as 1953 it was recognized that an implanted material must not be modified by body fluids and must be chemically inert. This commonsense directive and the susceptibility of PP to chemical transformation via oxidation both *in vivo* and *in vitro*, which—as documented above—was known at the time the Ethicon pelvic mesh products were designed and manufactured.

The literature clearly shows that the properties of polypropylene mesh change after implantation, causing adverse events like pain, scarring, and inflammation [40]. These injuries are directly caused by the change of the intended chemical and performance make-up of polypropylene mesh. Stiffening or reduced compliance of the polypropylene pelvic mesh upon degradation has important implications on the intended performance of the mesh as a biomaterial. The stiffness of a biomaterial implant must be compatible with the tissues with which it comes into permanent contact – this is fundamental to biocompatibility [44]. The mesh is designed to be soft and flexible and move with the soft pelvic tissue. However, as the polypropylene mesh undergoes oxidative degradation it becomes stiffer, much stiffer than the pelvic tissue. When a force is applied to this mesh/tissue interface the softer tissue moves but the mesh does not. This creates a shear force on

the tissue [45] akin to running a polypropylene fiber (monofilament fishing line) back and forth over skin. Consequently, based on the available scientific literature, the effect of relative movement between the polypropylene pelvic mesh that has undergone chemical changes, degradation, and reduced compliance and the surrounding tissue is a destructive effect to tissue, leading to pain, inflammation, and possible erosions.

Before launching its SUI and POP mesh products, Ethicon scientists concluded that the Prolene polypropylene degrades *in vivo*

Ethicon has reported evidence of PP oxidation and degradation since the 1980s. These internal documents report evidence of degradation of Prolene sutures, as well as instances of chronic inflammation and oxidation. In 1981, the depth of surface cracks (0.5-4.5 microns) was measured for explanted Prolene sutures [46]. Another document from 1983 reported cracking of explanted Prolene sutures [47], with one of the explanted sutures retaining only 54% of its original strength, and noting that the histological evaluation of explanted sutures was consistent with previous studies, characterized by a foreign body reaction and a "degraded acellular infiltrate." In this work Ethicon scientists used the same staining method employed by Iakovlev et al. [26] to stain the degraded polypropylene and confirm that the cracked layer was Prolene polypropylene and not biological material. This document also refers to a "Prolene Microcrack Committee". Thus, Ethicon was sufficiently aware of Prolene surface cracking and concerned enough about the consequences to form a committee to investigate the mechanism of cracking.

Two Ethicon memos from 1984 involved microcracking of explanted PP sutures from both ophthalmic and cardiovascular applications [48]. Sutures that were in the body for more than two years exhibited surface or severe transverse cracks ranging from 2 – 5 microns thick. Dr. Peter Moy of Ethicon wrote in another 1984 report that "oxidative degradation is another mechanism through which transverse cracks may be produced on oriented fibers" [49]. To try and reproduce the observed cracking *in vitro*, Prolene sutures were incubated in aqueous 30% hydrogen peroxide for up to a year. While transverse cracks were not observed, IR spectroscopy revealed the presence of oxidation products, which led Dr. Moy to conclude that "the possibility of a highly specific *in vivo* oxidation process remains." His conclusion is correct - the foreign body reaction actually produces a stronger oxidizing environment than 30% hydrogen peroxide alone [50], thus cracking may occur within the body while no cracking is observed in the

presence of peroxide. Dr. Moy also cited thermal stability and electron microdiffraction data to support his hypothesis that at least a portion of the cracked layer contained protein. He recommended an additional study to test this hypothesis by performing TEM analysis of known oxidized Prolene samples. A memo dated November 13, 1984 by Mr. Dan Burkley of Ethicon, reported that Prolene microcracks were evaluated using Attenuated Total Reflectance (ATR) and FTIR. These investigations revealed that the cracked Prolene surface was a composite of oxidized polypropylene and absorbed protein [51].

In 1985, a series of experiments, including FTIR, TEM, and histology, were performed to determine the clinical functionality of cracked sutures, the cracking mechanism, and effects of anti-oxidant concentration [52]. Dr. Moy noted that laboratory experiments had not replicated the cracking observed in explants, and proposed a systematic evaluation of explanted Prolene sutures.

In 1987, Ethicon was provided with explanted sutures, which had been cleaned using bleach solution as explained in Mr. Burkley's laboratory notebook [53]. SEM images of sutures implanted for 8 years revealed severe cracking. Scrapings were taken from explanted sutures and tested using calorimetry and FTIR. The waxy scrapings showed a melting point of 147 – 156 ^{o}C, and noted "This is the melting range previously observed for oxidatively degraded polypropylene." Non-degraded Prolene melts over the range 155 – 165 ^{o}C. Scrapings were also melted onto a KBr window in order to obtain FTIR spectra, which showed peaks of β-keto esters, which are known to be formed during polypropylene oxidation. Mr. Burkley noted that "no protein species or peptide bonds were suggested." A memo reporting on a follow-up meeting confirmed the findings that no protein was found on the surface and that Prolene degradation occurred on the surface of the fibers [54]. Several follow-up studies were proposed, including investigating the relationship between anti-oxidant concentration and polypropylene degradation and cracking. It is not clear whether or not these studies were ever performed.

In 1992 an Ethicon memo on 7 Year Data for 10 Year Prolene Study by Lindemann, Muse, and Burkley [55] reported "IR spectra obtained for cracked Prolene specimens (Figure A) showed possible evidence of slight oxidation…" and noted that "degradation in Prolene is still increasing".

Ethicon was also informed of the risks inherent to using polypropylene in an implantable medical device through the Material Safety Data Sheet (MSDS), which states that polypropylene is incompatible with strong oxidizers [56]. As explained above, implanted mesh is exposed to reactive oxygen species, which are strong oxidizers, as a result of the foreign body reaction. The report from Ethicon's Mesh Repair of Uterovaginal Prolapse meeting in May 1997 noted that an ideal mesh would have a lower density, in order to minimize the foreign body reaction [57]. Similar concerns were noted in a document on the design of new mesh for prolapse repair, in which it was noted that Prolene polypropylene mesh is not the ideal material for anterior prolapse, and that the amount of foreign body reaction should be minimized to reduce the risk of complications [58].

Despite internal and published studies, noted above, to the contrary, Ethicon documents further indicate that their sales force was instructed to "[r]eassure [surgeons] that PROLENE is proven to be inert and there are hundreds of papers going back 25 years to reinforce this point" [59]. However, Mr. Dan Burkley, a Principal Scientist at Ethicon, testified that in his 34 years at the company, he was only familiar with one study that was conducted regarding the changes that occurred due to oxidative degradation of explanted polypropylene suture or mesh [60]. Mr. Burkley also testified that this study showed that changes due to oxidation were still progressing after seven years of implantation [61]. Finally, Dr. Thomas Barbolt, a former Ethicon scientist, testified that the Prolene polypropylene used by Ethicon in manufacturing its SUI and POP meshes undergoes surface degradation while implanted in the human body and that Ethicon knew this several years before claiming in its IFU that the material is not "subject to degradation" [62].

Summary

In summary, polypropylene is susceptible to oxidative degradation and this degradation takes place *in vivo*, resulting in degradation of polypropylene meshes, including Ethicon's Prolene-based polypropylene meshes, which are used as permanent implants in pelvic surgery. There is a linear causative chain established by the scientific literature from polypropylene's chemical characteristics, its degradation, degradation's effect on the polypropylene rendered into

a mesh, and the effects to the human body. The process of oxidative degradation of polypropylene is tested and established chemistry. Thus, the more than half-century old rationale of adding anti-oxidants to polypropylene. Likewise, the process of oxidative degradation in vivo of polypropylene is tested, studied, and published. This established science includes studies specifically of Prolene polypropylene. The scientific evidence establishes that upon implantation the polypropylene implant is detected as a foreign material within the body causing the foreign body response. This leads to the release of strong reactive oxygen species and oxidative enzymes in the vicinity of the implant. This in turn leads to an oxidative degradation process, which may be delayed but not prevented by addition of anti-oxidants, which is detected by the appearance of hydroxyl and then carbonyl groups in the polypropylene, as evidenced by infrared spectra. There is accompanying degradation of the polypropylene molecular weight. This degradation, which will continue as long as the implant is in the body, is accompanied by a decrease in the mechanical properties of the implant. In particular, the surface and amorphous regions of the polypropylene are selectively degraded, resulting initially in cracks, flaking, and on longer exposure fragmentation of the implant. The polypropylene implant also stiffens in response to oxidative degradation. This creates a mechanical mismatch with the surrounding tissue that can lead to pain, inflammation, and tissue damage in patients implanted with the device.

From a materials science and polymer engineering perspective, Ethicon's Prolene polypropylene, as utilized in all Ethicon pelvic mesh products to treat SUI or POP, foreseeably cannot perform as intended, where intended, for as long as intended, posing a substantial risk for the person for whom it is intended, and is thus unreasonably dangerous to sell for the uses Ethicon sold it for. Ethicon was unreasonable, based on the scientific and engineering knowledge available, to sell these devices for the intended applications.

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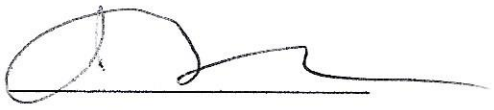

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April 29, 2016

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